REMARKS

Claims 5-8, 11, 23, 24, 44-48, 51 and 54-57 presently appear in this case. No claims have been allowed. All of the claims previously withdrawn from consideration have now been deleted without prejudice toward the filing of a divisional application thereon. The official action of December 2, 2004, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to DNA encoding a polypeptide that potentiates cell death and has the sequence of SEQ ID NO: 1, as well as analogs and fragments thereof. The invention also relates to vectors and host cells containing the DNA, polypeptides encoded by the DNA, and methods of producing the polypeptides using such a host cell, as well as the pharmaceutical compositions. The present invention is also directed to oligonucleotide molecules consisting of an antisense sequence of at least a part of an mRNA encoding a polypeptide of the present invention and a pharmaceutical composition containing such oligonucleotide.

The examiner states that the substitute specification submitted on February 28, 2002, lacks references 53-75 cited in the original specification. Applicants' file copy of the substitute specification includes page 65, which has references 53-75. Apparently this page must have become

inadvertently detached from the PTO copy of the substitute specification. The present amendment adds the text of originally-filed page 65 so as to complete the substitute specification. No new matter is presented as all of these citations appeared in the specification as originally filed.

The examiner states that the application contains sequence disclosures but that the application fails to comply with the requirements of 37 C.F.R. §1.821-25. The examiner states that the cited sequences in the specification are not accompanied by SEQ ID NOs at Figure 3's legend on page 18 and the sequence cited on page 38.

The examiner's attention is invited to the supplemental amendment of May 14, 2004, which amends the specification in the paragraph beginning on line 8 of page 18, that discusses Figure 3, to add reference to SEQ ID NO:1 and SEQ ID NO:2. Private PAIR shows that the Patent and Trademark Office has received this supplemental amendment. It is respectfully requested that the examiner acknowledge this receipt and withdraw the requirement with respect to this paragraph.

With respect to the sequence cited on page 38, a new sequence identifier has been added to this sequence, i.e., SEQ ID NO:3. Accordingly, applicants have added into the present specification a new paper copy Sequence Listing section

according to 37 C.F.R. §1.821(c) as new pages 1-5 to take into account SEQ ID NO:3.. Furthermore, attached hereto is a 3 1/2" disk containing the "Sequence Listing" in computer readable form in accordance with 37 C.F.R. §1.821(e). The paper and computer readable form are attached hereto as Appendix A.

The following statement is provided to meet the requirements of 37 C.F.R. §1.821(f) and 1.821(g) §1.825(a) and 1.825(b).

I hereby state, in accordance with 37 C.F.R. §1.825(a), that the amendments included in the substitute sheets of the sequence listing are believed to be supported in the application as filed and that the substitute sheets of the sequence listing are not believed to include new matter.

I hereby further state, in accordance with 37 C.F.R. §1.825(b), that the attached copy of the computer readable form is the same as the attached substitute paper copy of the sequence listing.

Under U.S. rules, each sequence must be classified in <213> as an "Artificial Sequence", a sequence of "Unknown" origin, or a sequence originating in a particular organism, identified by its scientific name.

Neither the rules nor the MPEP clarify the nature of the relationship which must exist between a listed sequence

and an organism for that organism to be identified as the origin of the sequence under <213>.

Hence, counsel may choose to identify a listed sequence as associated with a particular organism even though that sequence does not occur in nature by itself in that organism (it may be, e.g., an epitopic fragment of a naturally occurring protein, or a cDNA of a naturally occurring mRNA, or even a substitution mutant of a naturally occurring sequence). Hence, the identification of an organism in <213> should not be construed as an admission that the sequence *per se* occurs in nature in said organism.

Similarly, designation of a sequence as "artificial" should not be construed as a representation that the sequence has no association with any organism. For example, a primer or probe may be designated as "artificial" even though it is necessarily complementary to some target sequence, which may occur in nature. Or an "artificial" sequence may be a substitution mutant of a natural sequence, or a chimera of two or more natural sequences, or a cDNA (i.e., intron-free sequence) corresponding to an intron-containing gene, or otherwise a fragment of a natural sequence.

The examiner should be able to judge the relationship of the enumerated sequences to natural sequences by giving full consideration to the specification, the art

cited therein, any further art cited in an IDS, and the results of his or her sequence search against a database containing known natural sequences.

Claims 51 and 53 have been rejected under 35 U.S.C. §101 because the claimed invention is directed to non-statutory subject matter. The examiner states that these claims do not distinguish over oligonucleotides as they exist naturally. The examiner states that the claims should be amended to indicate the hand of the inventor, for example, by insertion of "isolated" or "purified".

Claims 51 and 53 have now been amended as suggested by the examiner, thus obviating this rejection.

Claims 8 and 11 have been rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for an isolated transformed eukaryotic host cell containing a vector according to claim 5, it is not reasonably enabled for a transformed eukaryotic host cell containing a vector according to claim 5. The examiner states that one cannot extrapolate the teaching in the specification to the scope of the claims as the claims read on *in vivo* target cells. The examiner states that the state of the art with respect to gene therapy was unpredictable at the time of filing the present application and, in view of the unpredictability of gene therapy and the lack of disclosure of

how to successfully produce *in vivo* host cells that express the claimed sequence, it would be undue experimentation for one of skill in the art to practice the claimed invention. This rejection is respectfully traversed.

Claim 8 is a product claim. The examiner concedes that applicants disclose how to make transformed eukaryotic or prokaryotic host cells containing a vector according to claim 5 *in vitro*. One only needs to disclose one way to make a product in order to claim the product. This is not a product-by-process claim. The fact that such host cells may be made by other methods does not require that the product claim be limited to the method disclosed. Furthermore, the fact that the examiner has cited references showing that there are problems hampering successful gene therapy does not mean that one of ordinary skill in the art could not get a vector according to claim 5 into a cell *in vivo*. The product claim does not require any particular method of use. Only a single utility is necessary for a product claim. The fact that it may be suitable for other allegedly non-enabled utilities is irrelevant. Reconsideration and withdrawal of this rejection of claim 8 are therefore respectfully urged.

New claim 55 has now been added that is the same as claim 8 but specifying that the cells are isolated. This claim is not subject to the present rejection as it cannot

read on *in situ* target cells. Claim 11 has been amended to depend from claim 55. Thus, this rejection no longer applies to claim 11. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 5-8, 11, 23, 24, 44-48, 51 and 52 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement for a DNA sequence encoding a polypeptide analog or fragment of SEQ ID NO:1, which analog or fragment potentiates cell death. This rejection is again respectfully traversed.

This issue is now ripe for appeal. Applicants again incorporate by reference the arguments made in the amendment of October 7, 2003, at pages 15-23.

The examiner appears to be of the opinion that, while mutagenesis and cell death assays are routine in the art, without a teaching of which amino acids to mutagenize or delete or substitute or add such that the claimed analogs will predictably potentiate cell death, one would not know how to make the claimed analogs or fragments. This argument ignores the fact that it is not necessary to be able to predict which analogs or fragments will potentiate cell death, as long as it would not take undue experimentation to test each of them. Furthermore, while the references cited by the examiner certainly establish that one amino acid change in the right place can affect the utility of a protein, these references

certainly do not establish that every such change, or even a majority of such changes, or even a large number of such changes would be expected to affect the utility of the protein. It is an evolutionary fact that mutations are occurring all the time throughout the genome of a living organism, but it is only a very infrequent situation where any such mutation will actually affect the utility of a particular gene and either cause a disease or threaten life. The claims read on mutations causing changes to only fewer than 2% of the total amino acids. Such mutations can be made and readily tested, as the examiner concedes. Substantial experimentation is expected in the biotechnology art, and there is no reason to believe that such experimentation would be undue. For all of these reasons, including the reasons of record, reconsideration and withdrawal of this rejection is respectfully urged.

Claims 24 and 51 have been rejected under 35 U.S.C. §102(e) as being anticipated by U.S. patent 5,578,468 to Pickup et al. The examiner states that the claim uses the term "corresponding", but there is no definition of this term in the specification. Therefore, any mRNA sequence would "correspond" to a DNA sequence of claim 44. The examiner also states that the language "at least part of" encompasses any length. The examiner states that Pickup teaches a sequence

that is 100% identical to the sequence at nucleotides 2067-2098 of SEQ ID NO:2 and, therefore, anticipates the claim. This rejection is respectfully traversed.

Claim 24 has now been amended to specify that the oligonucleotide molecule consists of "an antisense sequence of at least part of a DNA sequence encoding the polypeptide of SEQ ID NO:1." The portion of SEQ ID NO:2 to which the oligonucleotide of Pickup corresponds is not part of the coding sequence. Thus, it is not "an antisense sequence of at least part of a DNA sequence encoding the polypeptide of SEQ ID NO:1." SEQ ID NO:2 includes a sequence that encodes the polypeptide of SEQ ID NO:1, but nucleotides 2067-2098 are not part of that part of SEQ ID NO:2 that encodes the polypeptide of SEQ ID NO:1. This new language in claim 24 is supported by the present specification in the paragraph beginning at page 13, line 16, which refers to "an oligonucleotide sequence which is an antisense sequence for at least part of the DNA sequence encoding a B1 protein of the invention."

Furthermore, claim 24 has been amended to specify "said part of the DNA sequence being of sufficient length to effectively block the expression of said polypeptide upon use." This language is supported by the present specification at page 32, lines 10-12, which refers to "oligonucleotides having the anti-sense coding sequence for the B1 proteins of

the invention, which would effectively block the translation of mRNAs encoding the proteins and thereby block their expression and lead to the inhibition of the (cell death) undesired effect." Thus, it is clear that the oligonucleotides must have the effect of blocking the expression of the protein. The polyA sequence of Pickup would have no such effect as it does not correspond to any portion of the mRNA that encodes the protein of SEQ ID NO:1.

Claim 51 has been similarly amended and is thus free of this rejection for the same reasons. Furthermore, new claims 56 and 57 have been added that are the same as claims 24 and 51 but specify that the oligonucleotide molecule consists of "an antisense sequence of at least a part of an mRNA sequence encoding the polypeptide of SEQ ID NO:1." This language is supported by the paragraph beginning at page 14, line 23, of the present specification, which refers to "an oligonucleotide sequence which is an antisense sequence of the B1 protein mRNA sequence." The term "corresponding to" no longer appears in any of these claims. Accordingly, reconsideration and withdrawal of this rejection are also respectfully urged.

It should be noted that claims 44-47 have been amended to use the "consisting essentially of" language previously appearing in claim 48. This language clarifies

claim 44 to ensure that it encompasses the sequence of SEQ ID NO:2.

All of the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. §112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By _____
Roger L. Browdy
Registration No. 25,618

RLB:rd
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\I\inl2\Wallach24\Pto\AmendmentI.doc